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Everolimus Plus Exemestane for the Treatment of Advanced Breast Cancer: A Review of Subanalyses from BOLERO-2[1]

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Abstract

Hormone receptor–positive breast cancer is typically managed with endocrine therapies. However, resistance to endocrine therapy results in disease progression in a large proportion of breast cancers. Through the understanding of the mechanisms of endocrine resistance, identification of implicated pathways and targets has led to the development of novel agents targeting these pathways. Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway aberrations are common in breast cancer, with increased PI3K/AKT/mTOR signaling associated with resistance to endocrine and human epidermal growth factor receptor 2 (HER2)–targeted therapies. The mTOR inhibitor everolimus, in combination with exemestane, has been approved for patients with advanced hormone receptor–positive/HER2-negative breast cancer who progress on prior nonsteroidal aromatase inhibitor therapy based on results reported in the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study. This review will summarize the overall findings from BOLERO-2 and will consider available subanalyses by age, Asian origin, visceral or bone metastases, and prior therapy, with the aim of identifying populations most likely to benefit from everolimus therapy. The review will also summarize safety findings and their management and the effects of everolimus on quality of life.

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Introduction

Breast cancer is the leading cause of cancer death among women worldwide [1]. In the United States in 2014, more than 232,670 women will be diagnosed with breast cancer and 40,000 are predicted to die of this disease [2].

Approximately 75% of breast cancers are hormone receptor–positive [3,4] and are typically managed with endocrine therapies, including aromatase inhibitors and selective estrogen receptor modulators [5,6]. However, primary or acquired resistance to endocrine therapy results in disease progression in a large proportion of breast cancers [7,8]. Through the understanding of the mechanisms of endocrine resistance, identification of implicated pathways and targets has led to the development of novel agents targeting these pathways [9–12].

Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway aberrations are common in breast cancer [13], with activating mutations in *PIK3CA* present in about one quarter of breast cancers [13–15]. PI3K/AKT/mTOR pathway abnormalities are present in both primary tumors and metastases [16,17], and increased PI3K/AKT/mTOR signaling is associated with resistance to endocrine and human epidermal growth factor receptor 2 (HER2)–targeted therapies and relapse [18–21].

Abbreviations: AE, adverse event; BSAP, bone-specific alkaline phosphatase; CBR, clinical benefit rate; CR, complete response; CTX, C-terminal cross-linking telopeptide of type 1 collagen; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NIP, noninfectious pneumonitis; ORR, objective response rate; PI3K/AKT/mTOR, phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; PFS, progression-free survival; P1NP, amino-terminal propeptide of type 1 collagen; PR, partial response; QoL, quality of life; TDD, time to definitive deterioration

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The mTOR inhibitor everolimus, in combination with exemestane, has been approved for patients with advanced hormone receptor–positive/HER2-negative (HER2 –) breast cancer who progress on prior endocrine therapy with either letrozole or anastrozole [22], based on the results from the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study [23,24]. This review will summarize the overall findings from BOLERO-2 and will consider available subanalyses and safety findings, with the aim of identifying populations most likely to benefit from everolimus therapy.

Primary Findings from BOLERO-2

The BOLERO-2 study was an international, double-blind, randomized, phase III study comparing everolimus plus exemestane to placebo plus exemestane in postmenopausal women with hormone receptor–positive/HER2 – advanced breast cancer progressing during or following nonsteroidal aromatase inhibitor therapy with either letrozole or anastrozole, defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment for advanced disease [23]. Patients received open-label exemestane and were randomly assigned to blinded therapy with either everolimus or placebo, and randomization was stratified according to the presence of visceral metastases and sensitivity to prior hormonal therapy [24]. Inclusion criteria allowed disease recurrence during or within 12 months after completion of adjuvant endocrine therapy, one prior line of chemotherapy for advanced breast cancer, and disease progression within 1 month after treatment for advanced breast cancer [23].

The primary end point of BOLERO-2 was progression-free survival (PFS) based on local assessment, and secondary end points included overall survival, objective response rate (ORR), quality of life (QoL), bone markers, and safety [23,24]. Tumors were evaluated by Response Evaluation Criteria In Solid Tumors (version 1.0) based on investigator assessment and supported by an independent radiology committee (central assessment).

BOLERO-2 included 724 patients (485 in the everolimus plus exemestane arm; 239 in the placebo plus exemestane arm) [23]. Baseline patient and disease characteristics are summarized in Table 1. At the final analysis after a median follow-up of 18 months, median PFS based on investigator assessment (local assessment) was 7.8 months in the everolimus plus exemestane arm and 3.2 months in the placebo plus exemestane arm [hazard ratio (HR), 0.45; 95% confidence interval (CI), 0.38-0.54; $P < .0001$; Table 2] [24]. Consistent results based on independent central assessment were observed (11.0 *vs* 4.1 months; HR, 0.38; 95% CI, 0.31-0.48; $P < .0001$).

Secondary end points from BOLERO-2 also favored everolimus plus exemestane therapy. ORR [complete response (CR) or partial response (PR)] was 12.6% (95% CI, 9.8-15.9) in the everolimus plus exemestane arm and 1.7% (0.5-4.2) in the placebo plus exemestane arm ($P < .0001$; local assessment) [24]. Median duration of overall response was 10.5 months (95% CI, 8.2-21.9) in the everolimus plus exemestane arm and 6.9 months (95% CI, 4.2-6.9) in the placebo plus exemestane arm [31]. Because the proportion of patients with a tumor response in each treatment arm was low, overall median time to response could not be determined for the overall population. Among patients with a CR or PR, the median time to response was 2.8 months (range, 1.2-19.4 months) in the everolimus plus exemestane arm and 5.0 months (range, 1.3-12.2 months) in the placebo plus exemestane arm [31]. Clinical benefit rate (CBR; CR + PR + stable disease for ≥ 24 weeks) was 51.3% (95% CI, 46.8-55.9) and 26.4% (95% CI, 20.9-32.4) in the everolimus plus exemestane and placebo plus exemestane arms, respectively ($P < .0001$; by local assessment) [24]. Median overall survival was 31.0 months (95% CI, 28.0-34.6) with everolimus plus exemestane and 26.6 months (95% CI, 22.6-33.1) with placebo plus exemestane (HR, 0.89; 95% CI, 0.73-1.10; stratified log-rank $P = .1426$) [32]. The authors highlighted some potential reasons for the lack of statistical significance in overall survival [32]. One reason was that there was a lack of power to detect a realistic overall survival advantage because the chosen sample size was based on the primary end point of PFS. Additionally, clinicians may have been able to determine if patients were not receiving study treatment due to the absence of adverse events (AEs) associated with mTOR inhibitors (e.g., stomatitis), and this may have encouraged the initiation of more aggressive treatments (e.g., chemotherapy) after progression [32].

The most commonly reported AEs (affecting > 30% of patients) in the everolimus plus exemestane arm included stomatitis (59% and 12% in the everolimus plus exemestane and placebo plus exemestane arms, respectively), rash (39% and 7%), fatigue (37% and 27%), diarrhea (34% and 19%), nausea (31% and 29%), and decreased appetite (31% and 13%) [24]. Half of the patients in the everolimus plus exemestane arm experienced grade 3/4 AEs, with 27% of patients in the placebo plus exemestane arm reporting grade 3/4 AEs [22]. The most common grade 3/4 AEs with everolimus plus exemestane compared to placebo plus exemestane included stomatitis (8% and < 1%), gamma-glutamyltransferase increase (7% and 7%), anemia (7% and 1%), hyperglycemia (5% and < 1%), fatigue (4% and 1%), and dyspnea (5% and 1%) [24].

Table 1. Summary of Baseline Patient and Disease Demographics in BOLERO-2 [24,25]

	Everolimus Plus Exemestane	Placebo Plus Exemestane
Overall	*n* = 485	*n* = 239
Median age (range), years	62 (34-93)	61 (28-90)
≥65 years, %	40	33
≥70 years, %	25	18
Ethnicity, %		
White	74	78
Asian	20	19
Black	3	1
Other	3	2
Visceral disease, %	58	59
Metastatic site, %		
Lung	30	33
Liver	33	30
Bone	77	77
Setting of most recent treatment, %		
Adjuvant	21	16
Advanced/metastatic disease	79	84
Prior therapy, %		
Letrozole/anastrozole as most recent therapy	74	75
Tamoxifen	47	50
Fulvestrant	17	16
Chemotherapy (any setting)	69	65
Chemotherapy (for metastatic disease)	26	26
Radiotherapy	70	69
Number of prior therapies, %		
1-2	46	47
≥3	54	53

* Prior therapies include those used in the adjuvant setting or to treat advanced disease.

Table 2. Summary of PFS Results for BOLERO-2, Including the Primary Analysis and Subanalyses

	Everolimus + Exemestane, Median PFS, Months	Placebo + Exemestane, Median PFS, Months	HR	95% CI	*P* Value
Overall population [24]	7.8	3.2	0.45	0.38-0.54	<.0001
Elderly [25]					
≥65 years	6.8	4.0	0.59	0.43-0.80	–
≥70 years	6.8	1.5	0.45	0.30-0.68	–
<65 years	8.3	2.9	0.38	0.30-0.47	–
Prior therapy					
Chemotherapy [26]	6.1	2.7	0.38	0.27-0.53	–
Adjuvant therapy [26,27]	11.5	4.1	0.39	0.25-0.62	–
Visceral disease [28]					
Yes	6.8	2.8	0.47	0.37-0.60	<.05
No	9.9	4.2	0.41	0.31-0.55	<.05
Bone-only metastases [28]	12.9	5.3	0.33	0.21-0.53	<.05
Ethnicity [29]					
Asian	8.5	4.1	0.62	0.41-0.94	–
Non-Asian	7.3	2.8	0.41	0.33-0.50	–
ILC [30]	6.9	4.2	0.59	0.37-0.95	–

CI, confidence interval; HR, hazard ratio; ILC, invasive lobular carcinoma; PFS, progression-free survival. Note: All analyses are based on investigator (local) assessment at the final analysis at a median follow-up of 18 months.

Subanalyses from BOLERO-2

Patient numbers in the populations included in the subanalyses are summarized in Table 1, and median PFS results for the individual subanalyses are summarized in Table 2. As summarized in the final PFS analysis of BOLERO-2 after a median follow-up of 18 months, the effect of everolimus plus exemestane treatment was consistent across subgroups defined by patient characteristics and prior therapy (estimated HR of 0.25 and 0.62, respectively), with everolimus plus exemestane increasing PFS benefits compared with placebo plus exemestane regardless of baseline disease or prior therapy characteristics [24]. These findings and other subanalyses are described in more detail in the following section.

Elderly Patients

The median age for breast cancer diagnosis in North America is 61 years [33,34]; more than 40% of patients with breast cancer are aged ≥65 years [34] and approximately 10% are aged >80 years [35]. Although breast cancer incidence and deaths in females aged >65 years is higher than in younger age groups [36], the limited availability of randomized studies in elderly patients hinders selection of optimal treatment in this patient population, particularly in those with comorbidities and susceptibility to AEs [25].

In BOLERO-2, protocol-specified analyses included results for patients aged ≥65 years (38% of those in the study or 275/724 patients), while analyses for those aged ≥70 years (23% of those in the study or 164/724 patients) were exploratory [25]. Disease and pretreatment characteristics were generally comparable between elderly (≥65 years) and younger (<65 years) age groups. Baseline performance status of the elderly population was slightly worse than that of younger patients. In addition, previous use of neoadjuvant/adjuvant chemotherapy was less common in older patients, and there were differences in rates of certain comorbidities (such as respiratory system abnormalities, metabolic and nutritional disorders, and vascular disorders) between the two populations.

PFS results favored everolimus plus exemestane treatment in the age-defined subgroups (≥65 years, <65 years, 70 years) [25]. Median PFS in patients ≥65 years was 6.8 compared with 4.0 months (HR, 0.59; 95% CI, 0.43-0.80) in the everolimus plus exemestane and placebo plus exemestane arms, respectively. Similarly, median PFS in patients aged ≥70 years and <65 years in the everolimus plus exemestane and placebo plus exemestane arms, respectively, was 6.8 and 1.5 months (HR, 0.45; 95% CI, 0.30-0.68) and 8.3 and 2.9 months (HR, 0.38; 95% CI, 0.30-0.47).

CBR in the everolimus plus exemestane arm was greater than in the placebo plus exemestane arm in all age subgroups, respectively, with CBR rates of 41% *versus* 31% in patients aged ≥65 years, 36% *versus* 23% in those aged ≥70 years, and 58% *versus* 24% in those aged <65 years [25]. Similarly, ORR also favored everolimus plus exemestane over placebo plus exemestane in all age groups, respectively, with ORR rates of 9% *versus* 5% in those aged ≥65 years, 9% *versus* 7% in those aged ≥70 years, and 15% *versus* 0% in those aged <65 years [25].

Comparable safety profiles among older and younger patients were observed [25]. There was lower mean duration of everolimus exposure in older compared with younger patients, but the dose intensity remained similar among age groups. The incidence of AEs was similar among patients aged ≥65, ≥70, and <65 years, including stomatitis (53% *vs* 49% *vs* 63%, respectively), pneumonitis (15% *vs* 14% *vs* 17%), hyperglycemia (13% *vs* 12% *vs* 15%), and hypercholesterolemia (6% *vs* 7% *vs* 13%).

Results from this analysis showed that no dosage adjustment of initial dosing is required in elderly patients who have no other health concerns [22]. However, close monitoring is recommended for these patients, and the everolimus dose should be adjusted if appropriate as AEs occur.

Prior Therapy

Subpopulations of patients who progressed on anastrozole or letrozole and who were enrolled in BOLERO-2 included those whose disease recurred during or after neoadjuvant/adjuvant therapy and those who had one line of prior chemotherapy for advanced breast cancer [26]. The effect of prior therapy on outcomes from BOLERO-2 was assessed as an exploratory analysis [26,27].

Prior Chemotherapy. In BOLERO-2, 26% (186/724) of patients in the overall population received prior chemotherapy for advanced breast cancer, with 12% having received greater than or equal to three therapies before starting study treatment [26]. Of those patients who received prior chemotherapy, 48% (90/186) were treated with chemotherapy in the advanced setting and 52% (96/186) were treated in both the neoadjuvant/adjuvant and advanced disease settings. The incidence of visceral disease was higher for patients who had prior chemotherapy for advanced breast cancer compared with those who did not (67% *vs* 56%), and disease recurrence less than 6 months after initial diagnosis of advanced or metastatic breast cancer was noted in 32% of patients who received prior chemotherapy compared with 17% of patients who had not.

Median PFS increased in the everolimus plus exemestane arm *versus* the placebo plus exemestane arm in patients who received prior chemotherapy for advanced breast cancer (6.1 *vs* 2.7 months; HR, 0.38; 95% CI, 0.27-0.53) [26]. The most common AEs in patients who received prior chemotherapy were stomatitis (53% and 18% for everolimus plus exemestane and placebo plus exemestane, respectively), diarrhea (31% and 8%), rash (36% and 3%), and fatigue (35% and 25%). The most common grade 3/4 AEs in this subgroup were stomatitis (9% and 2%), hyperglycemia (6% and 0%), fatigue (4% and 2%), and pneumonitis (4% and 0%). The AE profile in patients

who underwent prior chemotherapy is consistent with the most common AEs reported in the overall population and the known safety profile of everolimus.

Prior Adjuvant Therapy

In BOLERO-2, approximately 20% of patients had disease recurrence during or within 12 months of completing adjuvant therapy (21% in the everolimus plus exemestane arm and 15% in the placebo plus exemestane arm), with almost all of these patients having letrozole or anastrozole as their last therapy before study entry (98% and 100%, respectively) [26,27]. Overall, 89% of patients in both arms were randomly assigned to the study <3 months from first recurrence; 137 patients received first-line everolimus plus exemestane (n = 100) or placebo plus exemestane (n = 37) in the advanced setting. Of these patients, 74% in the everolimus plus exemestane arm and 76% in the placebo plus exemestane arm recurred after adjuvant endocrine therapy plus chemotherapy, and 26% of patients in the everolimus plus exemestane arm and 24% in the placebo plus exemestane arm recurred after adjuvant endocrine therapy alone [26,27].

Everolimus plus exemestane increased median PFS compared with placebo plus exemestane (11.5 *vs* 4.1 months; HR, 0.39; 95% CI, 0.25-0.62) in patients who recurred after adjuvant therapy, suggesting efficacy as first-line everolimus therapy in the advanced setting [26,27]. Among patients who had undergone prior neoadjuvant/adjuvant treatment as the last prior therapy, valid data for target lesion diameters were available for 62 of 100 patients in the everolimus plus exemestane arm and 23 of 37 patients in the placebo plus exemestane arm, with decreases from baseline in the sum of the longest target lesion diameters by local assessment shown for 79% of patients with prior neoadjuvant/adjuvant therapy in the everolimus plus exemestane arm and 30% in the placebo plus exemestane arm [31].

The most common AEs in patients who recurred during or after adjuvant therapy were stomatitis (68% and 22% for everolimus plus exemestane and placebo plus exemestane, respectively), diarrhea (40% and 22%), rash (37% and 8%), and fatigue (32% and 16%) [26,27]. The most common grade 3/4 AEs in this subgroup were hyperglycemia (8% and 3%), stomatitis (4% and 0%), diarrhea (4% and 0%), and fatigue (3% and 3%). This AE profile is consistent with the most common AEs reported in the overall population and the known safety profile of everolimus.

These findings with everolimus in both prior therapy subsets suggest that, compared with the overall population, everolimus is effective in patients who received prior chemotherapy for advanced breast cancer and had high tumor burden. The findings also provide support for first-line therapy with everolimus in combination with exemestane for disease recurrence during or after adjuvant nonsteroidal aromatase inhibitor therapy [26].

Visceral Disease

Many postmenopausal patients with hormone receptor–positive advanced breast cancer present with visceral metastases [37]. First metastasis is estimated to occur in the skeletal system in 46% of patients, in the visceral organs in 41%, and in both systems in 13%; disease remains in the bone or visceral organs in about 60% of patients and develops into bone and visceral metastases in greater than 40% of patients [38].

In an exploratory analysis of the BOLERO-2 study, the efficacy and safety of everolimus plus exemestane were evaluated according to the presence of visceral disease, which was reported in 56% (406/724) of patients in both treatment arms [28]. Of the patients with visceral disease, 84% had greater than or equal to two metastatic sites and 50% had greater than or equal to three metastatic sites [28]. Metastatic sites included the lung (in ~45% of patients), liver (50%), and metastases to both sites (14%).

Among patients with visceral metastases, median PFS was 6.8 months in the everolimus plus exemestane arm compared with 2.8 months in the placebo plus exemestane arm (HR, 0.47; 95% CI, 0.37-0.60; $P < .05$); among patients without visceral metastases, median PFS was 9.9 months in the everolimus plus exemestane arm compared with 4.2 months in the placebo plus exemestane arm (HR, 0.41; 95% CI, 0.31-0.55; $P < .05$) [28].

Improvements in PFS with everolimus therapy were seen in all patients irrespective of Eastern Cooperative Oncology Group (ECOG) performance status, with patients with visceral metastases and an ECOG performance status of 0 having a median PFS of 6.8 months in the everolimus plus exemestane arm *versus* 2.8 months in the placebo plus exemestane arm (HR, 0.54; 95% CI, 0.40-0.73; $P < .05$) [28]. In patients with visceral metastases and an ECOG performance status ≥1, the median PFS with everolimus plus exemestane was more than three times longer than that of placebo plus exemestane (6.8 *vs* 1.5 months, respectively).

CBR was significantly higher among patients treated with everolimus plus exemestane *versus* placebo plus exemestane, irrespective of visceral involvement (no visceral disease at baseline: 60% *vs* 32%, respectively; visceral disease at baseline: 45% *vs* 22%) [28]. Patients with visceral disease had a similar CBR with everolimus therapy independent of ECOG performance status.

Among patients with baseline visceral disease, valid data for target lesion diameters were available for 224 of 271 patients in the everolimus plus exemestane arm and 107 of 135 patients in the placebo plus exemestane arm, with decreases from baseline in the sum of the longest target lesion diameters by local assessment shown for 69% of patients with baseline visceral disease in the everolimus plus exemestane arm *versus* 27% in the placebo plus exemestane arm [31].

The incidence of AEs was generally similar in patients with or without visceral disease, with no increased risk of any specific AE in patients with visceral metastases [28]. The most common AEs for patients receiving everolimus with visceral *versus* nonvisceral disease were stomatitis (59% and 59%, respectively), rash (40% and 39%), fatigue (40% and 36%), decreased appetite (36% and 24%), and diarrhea (34% and 34%); this AE profile was consistent with the overall study population.

This subanalysis of BOLERO-2 highlights that everolimus in combination with exemestane may be a potential alternative to chemotherapy for patients whose visceral metastases are not immediately life threatening [28].

Bone Disease

The bone of patients with breast cancer may be adversely affected by both the disease and some breast cancer therapies [39,40]. The interaction of breast cancer and bone cells causes intracellular signaling that promotes the growth and spread of bone metastases, and breast cancer cells can secrete factors promoting osteolysis, causing bone destruction and tumor growth [39]. Endocrine therapies can also increase bone loss, thereby exacerbating bone-related complications in patients with breast cancer [40].

Because everolimus was used in combination with exemestane, which is known to increase bone turnover [40], exploratory analyses

of patients with and without bone-only disease, as well as patient bone turnover markers at 6 and 12 weeks, were performed in the BOLERO-2 trial [41]. The presence of bone metastases at baseline was comparable between treatment arms (77% in both arms), and baseline bisphosphonate use was less frequent in the everolimus plus exemestane arm *versus* placebo plus exemestane arm (44% and 54%, respectively) [41]. Progressive disease in the bone occurred in 13% of patients treated with everolimus plus exemestane compared with 19% treated with placebo plus exemestane [41].

Median PFS in patients with bone-only metastasis treated with everolimus plus exemestane and placebo plus exemestane was 12.9 and 5.3 months, respectively, indicating a 67% reduction in the risk of progression (HR, 0.33; 95% CI, 0.21-0.53; $P < .05$); this was similar to the risk reduction of 55% observed in the overall population (HR, 0.45; 95% CI, 0.38-0.54; $P < .0001$) [28].

Bone marker levels, including bone-specific alkaline phosphatase (BSAP), amino-terminal propeptide of type 1 collagen (P1NP), and C-terminal cross-linking telopeptide of type 1 collagen (CTX), increased at 6 and 12 weeks relative to baseline in the placebo plus exemestane arm, while levels decreased in the everolimus plus exemestane arm [41]. The differences between the everolimus plus exemestane and the placebo plus exemestane arms were significant from baseline to week 6 compared with the placebo arm [26% for BSAP; 56% for P1NP; 36% for CTX ($P < .001$ for all)]. Similar trends were observed at week 12 [20% ($P = .005$) for BSAP; 66% ($P < .001$) for P1NP; 41% ($P < .001$) for CTX]. Reductions in bone marker levels were observed irrespective of the presence of bone metastases or baseline bisphosphonate use.

The results suggest that combination therapy with everolimus and exemestane may help lower disease progression in the bone and may suppress increased bone turnover and resorption observed with exemestane monotherapy [41]. However, these observations are from exploratory analyses and need to be confirmed in larger trials, and it is currently unknown if the improvement in bone turnover is sustained throughout the duration of everolimus therapy.

Asian Subset

As the effect of anticancer treatments may be influenced by ethnicity, a post hoc analysis of the results from BOLERO-2 in Asian *versus* non-Asian patients was completed [29]. In the study, 20% of enrolled patients were Asian (143/724, with 74% being of Japanese origin), with 69% of Asian patients receiving everolimus and 31% placebo. Baseline patient and disease characteristics among Asian and non-Asian patients were comparable, but Asian patients were younger and had a better performance status than non-Asian patients. The median duration of exposure to treatment was longer in the Asian population.

Everolimus plus exemestane improved median PFS in Asian patients by 38% (HR, 0.62; 95% CI, 0.41-0.94) and in non-Asian patients by 59% (HR, 0.41; 95% CI, 0.33-0.50) [29]. Median PFS duration among Asian patients was 8.5 compared with 4.1 months in the everolimus plus exemestane and placebo plus exemestane arms, respectively, and among non-Asian patients, it was 7.3 compared with 2.8 months.

AEs reported more commonly in Asian patients compared with non-Asian patients receiving everolimus plus exemestane included stomatitis (80% and 54%, respectively), rash (50% and 37%), dysgeusia (31% and 20%), pneumonitis (23% and 15%), nail disorder (22% and ~4%), increased lactate dehydrogenase (14% and 4%), nasopharyngitis (22% and 7%), and interstitial lung disease (13% and <1%) [29]. Pneumonitis, which was reported only in the everolimus plus exemestane arm, was higher in Asian patients than in non-Asian patients, while the frequency of grade 3/4 pneumonitis was lower in Asian patients compared with non-Asian patients (2% *vs* 4%). The incidence of grade 3/4 AEs in the everolimus plus exemestane arm was similar or lower in Asian patients compared with non-Asian patients, apart from increased aspartate aminotransferase (6% *vs* ~3%) and cough (3% *vs* <1%), and there were very few grade 4 AEs reported, regardless of treatment arm or ethnicity.

This analysis suggests that everolimus provides substantial clinical benefit in both Asian and non-Asian patients, with similar safety profiles [29].

Invasive Lobular Carcinoma

Invasive lobular carcinoma (ILC) is less common than infiltrating ductal carcinoma (IDC) and has more favorable clinicopathologic parameters compared with IDC tumors [42,43]. However, ILCs have an increased propensity for multifocal and multicentric distribution, bilaterality, and different patterns of metastatic involvement compared with IDCs, and as a result, survival prognosis is generally worse [42,43]. An exploratory analysis of the BOLERO-2 study evaluated patients with ILC [30]. Upon local assessment, the median PFS was 6.9 months in the everolimus plus exemestane arm *versus* 4.2 months in the placebo plus exemestane arm, respectively (HR = 0.59; 95% CI, 0.37-0.95) [30]. The AE profile between the two treatment groups was similar to that of the overall study population.

Quality of Life

Although treatments for advanced breast cancer should maintain or improve QoL [44], disease- and treatment-related factors may adversely affect health-related QoL [45,46]. The health-related QoL effect of everolimus was assessed as a secondary end point in the BOLERO-2 study [44]. At a median follow-up of 18 months, time to definitive deterioration (TDD), defined as a 5% change from baseline European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 health status score, was higher with everolimus plus exemestane than with placebo plus exemestane (8.3 *vs* 5.8 months; $P = .0084$) [44]. Although TDD based on a 10-point minimally important difference, which is reported to be a relevant change in other cancer populations, was higher with the everolimus plus exemestane *versus* placebo plus exemestane arms, the difference was not statistically significant (11.7 *vs* 8.4 months; $P = .1017$) [44]. Greater benefits were found in patients with an ECOG performance status score of 1 or 2 and in those aged <65 years.

To further assess the impact of everolimus therapy on disease burden, additional post hoc analyses of health-related QoL outcomes from the BOLERO-2 trial at a median follow-up of 18 months have been reported [47]. In a sensitivity analysis assessing the effect of study discontinuation on or before week 24 of treatment, patients who discontinued early from the study had worse health-related QoL decline on both treatments, while patients treated with everolimus plus exemestane who did not discontinue early from the study had stable QoL outcomes compared with those receiving placebo plus exemestane.

Everolimus treatment did not affect QoL compared with placebo in Asian patients, with a median TDD of 8.4 months (95 % CI, 6.9-11.1) in the everolimus plus exemestane arm compared with

5.6 months (95% CI, 2.9-15.2) in the placebo plus exemestane arm (HR, 0.79; 97.5% CI, 0.44-1.44) [29].

The improvement in TDD of global health status with everolimus in combination with exemestane was shown despite a higher incidence of grade 3/4 AEs and discontinuations because of AEs with everolimus plus exemestane, and it is suggested that the clinical benefit of everolimus plus exemestane therapy may have contributed to this effect [44].

Exploratory Analysis of Biomarkers

A retrospective, exploratory analysis of the BOLERO-2 study evaluated genetic variations of cancer-related genes using next-generation sequencing from formalin-fixed, paraffin-embedded archival tissues collected during patient recruitment and explored the correlations of these genetic alterations with everolimus benefit [48]. Through the individual evaluation of alterations of the four most commonly mutated genes in this analysis (*PIK3CA*, *cyclin D1*, checkpoint gene *p53*, and *fibroblast growth factor receptor 1*) or their respective pathways, the PFS benefit of everolimus in patients with these altered pathways was similar to the PFS benefit seen in the overall study population [48].

However, when the data were sorted by minimal or multiple genetic alterations, patients with wild-type genes or only a single genetic alteration in the *PIK3CA*, *cyclin D1*, or *fibroblast growth factor receptors 1 and 2* gene (76% of the patients in this exploratory analysis) derived greater benefit from everolimus than the overall population (HR, 0.27; 95% CI, 0.18-0.41) [48]. In all, these data suggested a complex association between upstream and downstream components of the mTOR pathway and may help generate new hypotheses for combinations of novel targeted therapies after prospective validation in independent patient cohorts.

Tolerability Considerations for Everolimus Use in Breast Cancer

mTOR inhibitors are associated with a unique AE profile, which includes stomatitis, infection, rash, noninfectious pneumonitis (NIP), hyperglycemia, and hyperlipidemia, that is not commonly observed with endocrine therapies [49]. Of note, hyperglycemia and dyslipidemia are of special interest to postmenopausal women who are already at increased risk for age-related metabolic abnormalities. Most AEs with everolimus are not life threatening and are reversible with supportive care and with interruption and/or adjustment of everolimus dosing [50]. Available management strategies to minimize the occurrence and severity of AEs associated with everolimus have been described [49,51–53]; in patients with severe AEs, temporary interruption or dose reduction of everolimus is recommended, and discontinuation of therapy is recommended for grade 4 events (Table 3) [22].

Dose Intensity, Exposure, and Modifications

In BOLERO-2, the median duration of exposure to everolimus was 23.9 weeks (range, 1.0-123.3) at a median follow-up of 18 months, and the median dose intensity was 8.6 mg/day [24,49]. In the everolimus plus exemestane arm, 46% of patients had a relative everolimus dose intensity between 0.9 and <1.1, 19% of patients had a relative dose intensity between 0.7 and <0.9, and 17% of patients had a relative dose intensity between 0.5 and <0.70; this suggests that doses of the intended therapies were near the recommended optimal dose in the majority of patients [54].

Dose interruptions/reductions were required in 62% of patients treated with everolimus plus exemestane and in 12% treated with placebo plus exemestane [49]. Among the 1065 instances of dose interruptions/reductions with everolimus, there were 360 dose reductions and 705 dose interruptions. The median time to first dose reduction was 55 days (range, 6-483) in the overall population, the median duration of dose reductions for everolimus was 29 days (range, 1-672), and the median duration of dose interruption was 7 days (range, 1-41).

More patients in the everolimus plus exemestane arm required at least one dose interruption or reduction for AEs (≥1 dose interruption: 56% for everolimus, 15% for exemestane; ≥1 dose reduction: 38% for everolimus, <1% for exemestane) than did patients in the placebo plus exemestane arm (≥1 dose interruption: 10% for placebo, 5% for exemestane; ≥1 dose reduction: 3% for placebo, 0 for exemestane), with the greatest number of dose interruptions/reductions attributed to everolimus [49]. The most common AEs leading to dose interruptions/reductions in the everolimus plus exemestane arm were stomatitis (24%), pneumonitis (8%), alanine aminotransferase increase (5%), aspartate aminotransferase increase (4%), dyspnea (4%), blood creatinine increase (3%), and fatigue (3%) [49]. There was no predominant AE leading to dose interruptions/reductions in the placebo plus exemestane arm.

Treatment discontinuations because of treatment-emergent AEs were higher in the everolimus plus exemestane arm (26% for everolimus; 9% for exemestane) than in the placebo plus exemestane arm (5% for placebo; 3% for exemestane); pneumonitis (6%), stomatitis (3%), dyspnea (2%), and fatigue (2%) were the most common AEs leading to treatment discontinuation in the everolimus plus exemestane arm [49]. Full-dose everolimus was resumed within 2 weeks in 76% and within 3 weeks in 88% of patients who had dose interruptions/reductions, with a median time of 8 days (range, 2-333) to resumption of full-dose everolimus in patients who were able to resume study drug.

Among the 1065 instances of everolimus dose interruptions/reductions (705 dose interruptions; 360 dose reductions), 44% resolved with resumption of full dosing of everolimus at 10 mg/day and 76% resolved within 2 weeks, with most patients who resumed the full 10-mg everolimus dose doing so within 2 weeks [49]. A limited number of patients who underwent dose reductions because of AEs were able to reescalate everolimus to the 10 mg/day dose.

Stomatitis

Stomatitis associated with mTOR inhibitors occurs as aphthous-like lesions that are discrete, relatively shallow, well demarcated with surrounding erythematous margins [55–57], and most commonly occurring in nonkeratinized mucosa [53,58].

In BOLERO-2, the frequency of stomatitis (i.e., stomatitis and related events) was higher in the everolimus plus exemestane *versus* placebo plus exemestane arm (67% *vs* 12%), with grade 3 events occurring in 8% and <1% of patients, respectively; no grade 4 events were reported for either arm [49]. Greater than one third of grade ≥2 stomatitis events occurred in the first 2 weeks of everolimus therapy. In the 39 patients with grade ≥3 stomatitis, 97% had resolution to grade ≤1 following dose interruption/reduction after a median of 3.1 weeks and 82% had complete resolution after a median of 7.4 weeks.

As outlined in Table 3, management of everolimus-associated stomatitis includes dose interruptions/reductions, discontinuations, and medical therapy depending on severity [22].

Table 3. Management Recommendations for Nonhematologic AEs as Based on the BOLERO-2 Study Protocol [22]

Severity	Everolimus Dose Modification *	Management Recommendations
Stomatitis		
Grade 1	• No dose adjustment required	• Manage with nonalcoholic or saltwater (0.9%) mouthwash several times a day
Grade 2	• Temporary dose interruption until recovery to grade ≤1, then reinitiate everolimus at a lower dose • If recurrence at grade 2, interrupt dose until recovery to grade ≤1, and reinitiate everolimus at a lower dose	• Manage with topical analgesic mouth treatments with or without topical corticosteroids
Grade 3	• Temporary dose interruption until recovery to grade ≤1, then reinitiate everolimus at a lower dose	• Manage with topical analgesic mouth treatments with or without topical corticosteroids
Grade 4	• Discontinue everolimus	• Treat with appropriate medical therapy
NIP		
Grade 1	• No dose adjustment required	• Initiate appropriate monitoring
Grade 2	• Consider interruption of therapy and then reinitiate everolimus at a lower dose • Discontinue treatment if failure to recover within 4 weeks	• Rule out infection • Consider treatment with corticosteroids until symptoms improve to grade ≤1
Grade 3	• Interrupt everolimus until symptoms resolve to grade ≤1 • Consider reinitiating everolimus at a lower dose • If toxicity recurs at grade 3, consider discontinuation	• Rule out infection • Consider treatment with corticosteroids
Grade 4	• Discontinue therapy	• Rule out infection • Consider treatment with corticosteroids
Other nonhematologic toxicities (excluding metabolic events)		
Grade 1	• No dose adjustment if toxicity tolerable	• Initiate appropriate medical therapy and monitor
Grade 2	• No dose adjustment if toxicity tolerable • If toxicity intolerable, temporary dose interruption until recovery to grade ≤1, then reinitiate everolimus at the same dose • If toxicity recurs at grade 2, interrupt everolimus until recovery to grade ≤1, and then reinitiate everolimus at a lower dose	• Initiate appropriate medical therapy and monitor
Grade 3	• Temporary dose interruption until recovery to grade ≤1 • Consider reinitiating everolimus at a lower dose • If toxicity recurs at grade 3, consider discontinuation	• Initiate appropriate medical therapy and monitor
Grade 4	• Discontinue	• Treat with appropriate medical therapy
Metabolic events		
Grade 1	• No dose adjustment required	• Initiate appropriate medical therapy and monitor
Grade 2	• No dose adjustment required	• Manage with appropriate medical therapy and monitor
Grade 3	• Temporary dose interruption • Reinitiate everolimus at a lower dose	• Manage with appropriate medical therapy and monitor
Grade 4	• Discontinue everolimus	• Treat with appropriate medical therapy

* If a dose reduction is required, the suggested dose is about 50% lower than the dose previously administered.

Noninfectious Pneumonitis

NIP is a nonmalignant infiltration of the lungs associated with mTOR inhibitors [51,52,59] and is observed in radiographic findings as ground-glass opacity with or without focal consolidation predominantly in the lower lobes of the lungs [50,51]. Patients with NIP may be asymptomatic or have nonspecific respiratory symptoms, including dyspnea, cough, hypoxia, and (rarely) pleural effusion, thereby complicating diagnosis. Fever has also been reported, requiring infection to be excluded as a cause.

As outlined in Table 3, management of everolimus-associated NIP includes dose interruptions/reductions, discontinuations, and medical therapy depending on severity [22]. Because symptoms are often subtle and lung metastases may complicate diagnosis, it is recommended that a thorough medical history be obtained and alternative treatment for patients with chronic obstructive pulmonary disease or significant pulmonary fibrosis be considered [51].

In BOLERO-2, 20% of patients in the everolimus plus exemestane arm and <1% in the placebo plus exemestane arm experienced NIP, with grade 3 events occurring in 4% of patients treated with everolimus and one grade 4 event reported [49]. There were few early NIP events and no plateau in occurrence. About 25% of grade ≥2 NIP events occurred within the first 12 weeks of everolimus therapy. In patients with grade ≥3 NIP treated with everolimus plus exemestane, 80% experienced resolution to grade ≤1 after a median of 3.8 weeks and 75% experienced complete resolution after a median of 5.4 weeks.

Rash

mTOR inhibitor–induced rash typically occurs as maculopapular or acneiform lesions, often with pruritus [60], with skin color and/or nail color changes, dry skin, or eczema also reported [61]. The rash typically occurs on the trunk, scalp, face, and neck, with the extremities also commonly affected [60].

In BOLERO-2, the incidence of rash was 39% in patients treated with everolimus plus exemestane and 7% in patients treated with placebo plus exemestane [24]. Grade 3 rash occurred in 1% of patients treated with everolimus, and no patients experienced grade 4 rash [24]. Rash led to discontinuation of study treatment in 2% and 0% of patients in the everolimus plus exemestane and placebo plus exemestane arms, respectively [49].

As outlined in Table 3, management of everolimus-associated rash includes dose interruptions/reductions, discontinuations, and medical therapy depending on severity [22].

Hyperglycemia

mTOR is involved in glucose homeostasis, and mTOR inhibitors have an impact on glycemic control [62]. In BOLERO-2, fasting serum glucose was monitored before the start of everolimus therapy and periodically thereafter, with optimal glycemic control achieved before starting study therapy [49]. Hyperglycemia was managed with appropriate medical therapy and monitoring [22]. For grade ≥2 hyperglycemia events requiring dose modifications of study drug, biochemistry tests were repeated until recovery to the baseline value or to grade 1 [49]. These recommendations from BOLERO-2 are consistent with those from a task force of the National Cancer Institute Investigational Drug Steering Committee assessing hyperglycemia and hyperlipidemia with PI3K/Akt/mTOR inhibitors [63].

In BOLERO-2, a notable number of patients in both treatment arms had diabetes mellitus or impaired glucose tolerance at baseline (9% in the everolimus plus exemestane arm and 10% in the placebo plus exemestane arm); 16% of patients treated with everolimus experienced hyperglycemia or new-onset diabetes mellitus compared with 3% in the placebo arm [49]. Grade 3/4 events occurred in 6% and 1% of patients, respectively, and approximately 50% of the grade ≥2 events occurred in the first 6 weeks of everolimus therapy. Among patients with grade ≥3 events in the everolimus plus exemestane arm, 46% experienced resolution to grade ≤1 after a median of 29.1 weeks.

Hyperlipidemia

Because fat metabolism is regulated by the mTOR signaling pathway, mTOR inhibition may contribute to hyperlipidemia [62]. In BOLERO-2, hyperlipidemia and hypertriglyceridemia were treated according to local best clinical practice, and pretreatment status and dietary habits were considered during management [49]. Hyperlipidemia was monitored through fasting blood samples, and patients were monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other AEs as required in the product labels for 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors [49].

In BOLERO-2, there was a higher incidence of hyperlipidemia in patients treated with everolimus plus exemestane *versus* those treated with placebo plus exemestane (14% and 2%, respectively), with an incidence of grade 3/4 events of 1% and 0%, respectively [49]. A quarter of the patients treated with everolimus who experienced grade ≥3 hyperlipidemia had resolution of the event to grade ≤1, with a median time to resolution not assessable because of low event rates.

Hematological Considerations

Bone marrow suppression is a common toxicity observed with mTOR inhibitor therapy [50]. In phase II/III trials of everolimus in breast cancer, anemia was reported in 11% to 69%, thrombocytopenia in 12% to 60%, and neutropenia in 10% to 66% of patients receiving everolimus [50]. In BOLERO-2, the most common hematologic toxicities were decreases in hemoglobin (68% in the everolimus plus exemestane arm *vs* 40% in the placebo plus exemestane arm), white blood cells (58% *vs* 28%), platelets (54% *vs* 5%), lymphocytes (54% *vs* 37%), and neutrophils (31% *vs* 11%) [22]. Grade 3/4 hematologic events included decreased hemoglobin (7% in the everolimus plus exemestane arm *vs* 1% in the placebo plus exemestane arm), white blood cells (1% *vs* 6%), platelets (3% *vs* <1%), lymphocytes (12% *vs* 6%), and neutrophils (2% *vs* 2%), with grade 4 hematologic events occurring in both treatment arms (1% *vs* 3%).

Most hematologic events with everolimus were grade 1/2, which does not necessitate interruption of therapy [50]. For grade 3 events, interruption of everolimus therapy and resumption at a lower dose is recommended. For grade 4 events, discontinuation of everolimus therapy is recommended.

Infections

Everolimus has immunosuppressive effects that may predispose patients to bacterial, viral, or protozoal infections, including opportunistic infection or reactivation of prior infection [22,51]. Bacterial infections, invasive fungal infections, and hepatitis B virus reactivation in previously infected patients have been reported with everolimus treatment in various malignancies.

In BOLERO-2, 6.6% of patients treated with everolimus plus exemestane experienced grade 3/4 infection, with 84% of these patients having resolution of the infectious event to grade ≤1, with a median time to resolution of 3 weeks [49].

Conclusions and Future Directions

The BOLERO-2 trial demonstrated a clinically meaningful improvement in PFS with everolimus plus exemestane therapy in patients with hormone receptor–positive/HER2– advanced breast cancer [24,64], and the consistency of the results were demonstrated across all assessed subgroups [24]. This efficacy benefit with everolimus comes with an increased incidence of mTOR inhibitor–associated toxicities. However, the TDD of performance status and QoL were not statistically different between treatment groups [44]. In general, class-effect AEs apart from NIP had a relatively short time to onset, with incidence tapering off thereafter. Grade 3/4 AEs occurred at a low rate and most resolved to grade ≤1 fairly quickly, suggesting that management recommendations for everolimus-related AEs, which include dose interruptions/reductions, enable continued treatment in most cases [49].

The identification and management of mTOR-associated AEs are critical aspects of patient treatment and should be approached proactively through dose interruptions and reductions, with return to active treatment on resolution. This approach appears to adequately manage cases of stomatitis and rash, but more extensive measures for the management of NIP may be required. Education of both physicians and patients on the unique AE profile of everolimus is recommended. Baseline screening for suspected lung disease, hypercholesterolemia, or diabetes and optimization of the

management of preexisting medical conditions are likely to have a role in decreasing the severity and frequency of AEs [50].

Although BOLERO-2 has provided clinically relevant results for everolimus in combination with exemestane, an important consideration might be the selection of the most appropriate patients for everolimus therapy [65]. Considering the results of BOLERO-2, everolimus plus exemestane may be appropriate as a standard option in treating postmenopausal patients with hormone receptor–positive/HER2 – advanced breast cancer with prior exposure to nonsteroidal aromatase inhibitors who are medically fit, who would be followed closely by their oncologist, and who are aware of the toxicity profile and associated management strategies for everolimus [64]. Consideration of use of everolimus only in prior hormone-sensitive breast cancer that has developed acquired resistance to nonsteroidal aromatase inhibitors has been suggested [65], and further evidence in the first-line setting should be obtained. Importantly, the subanalyses of BOLERO-2 showed that the benefit of everolimus therapy was similar in patients with no prior therapy for advanced disease and in those with more heavily treated cancer. As such, there is currently no strong evidence that resistance to prior therapy is a requisite for the efficacy of everolimus, or that everolimus in combination with exemestane should only be considered for second- or third-line therapy of hormone receptor–positive/HER2 – advanced breast cancer. Further research is needed in hormone receptor–positive/HER2 – patient populations to further evaluate the appropriate patients that could be treated with everolimus.

References

[1] Ino Y, Kubo T, Tanaka A, Kuroi A, Tsujioka H, Ikejima H, Okouchi K, Kashiwagi M, Takarada S, and Kitabata H, et al (2011). Difference of culprit lesion morphologies between ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome: an optical coherence tomography study. *JACC Cardiovasc Interv* **4**, 76–82.

[2] American Cancer Society (2014). Cancer facts and figures 2014. Atlanta, GA: American Cancer Society; 2014 .

[3] Anderson WF, Chatterjee N, Ershler WB, and Brawley OW (2002). Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database. *Breast Cancer Res Treat* **76**, 27–36.

[4] Setiawan VW, Monroe KR, Wilkens LR, Kolonel LN, Pike MC, and Henderson BE (2009). Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. *Am J Epidemiol* **169**, 1251–1259.

[5] American Cancer Society (2013). Breast Cancer Facts and Figures 2013–2014. Atlanta, GA: American Cancer Society; 2013 .

[6] Cleator SJ, Ahamed E, Coombes RC, and Palmieri C (2009). A 2009 update on the treatment of patients with hormone receptor-positive breast cancer. *Clin Breast Cancer* **9**(Suppl. 1), S6–S17.

[7] Dodwell D, Wardley A, and Johnston S (2006). Postmenopausal advanced breast cancer: options for therapy after tamoxifen and aromatase inhibitors. *Breast* **15**, 584–594.

[8] Musgrove EA and Sutherland RL (2009). Biological determinants of endocrine resistance in breast cancer. *Nat Rev Cancer* **9**, 631–643.

[9] Osborne CK and Schiff R (2011). Mechanisms of endocrine resistance in breast cancer. *Annu Rev Med* **62**, 233–247.

[10] Rugo HS and Keck S (2012). Reversing hormone resistance: have we found the golden key? *J Clin Oncol* **30**, 2707–2709.

[11] Normanno N, Di Maio M, De Maio E, De Luca A, de Matteis A, Giordano A, Perrone F, and NCI-Naple Breast Cancer Group (2005). Mechanisms of endocrine resistance and novel therapeutic strategies in breast cancer. *Endocr Relat Cancer* **12**, 721–747.

[12] Xu Y and Sun Q (2010). Headway in resistance to endocrine therapy in breast cancer. *J Thorac Dis* **2**, 171–177.

[13] Liu P, Cheng H, Roberts TM, and Zhao JJ (2009). Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat Rev Drug Discov* **8**, 627–644.

[14] Bachman KE, Argani P, Samuels Y, Silliman N, Ptak J, Szabo S, Konishi H, Karakas B, Blair BG, and Lin C, et al (2004). The PIK3CA gene is mutated with high frequency in human breast cancers. *Cancer Biol Ther* **3**, 772–775.

[15] Saal LH, Holm K, Maurer M, Memeo L, Su T, Wang X, Yu JS, Malmström PO, Mansukhani M, and Enoksson J, et al (2005). PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. *Cancer Res* **65**, 2554–2559.

[16] Akcakanat A, Sahin A, Shaye AN, Velasco MA, and Meric-Bernstam F (2008). Comparison of Akt/mTOR signaling in primary breast tumors and matched distant metastases. *Cancer* **112**, 2352–2358.

[17] Gonzalez-Angulo AM, Ferrer-Lozano J, Stemke-Hale K, Sahin A, Liu S, Barrera JA, Burgues O, Lluch AM, Chen H, and Hortobagyi GN, et al (2011). PI3K pathway mutations and PTEN levels in primary and metastatic breast cancer. *Mol Cancer Ther* **10**, 1093–1101.

[18] Pérez-Tenorio G and Stål O (2002). Activation of AKT/PKB in breast cancer predicts a worse outcome among endocrine treated patients. *Br J Cancer* **86**, 540–545.

[19] Nagata Y, Lan KH, Zhou X, Tan M, Esteva FJ, Sahin AA, Klos KS, Li P, Monia BP, and Nguyen NT, et al (2004). PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. *Cancer Cell* **6**, 117–127.

[20] Berns K, Horlings HM, Hennessy BT, Madiredjo M, Hijmans EM, Beelen K, Linn SC, Gonzalez-Angulo AM, Stemke-Hale K, and Hauptmann M, et al (2007). A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer. *Cancer Cell* **12**, 395–402.

[21] Miller TW, Perez-Torres M, Narasanna A, Guix M, Stål O, Pérez-Tenorio G, Gonzalez-Angulo AM, Hennessy BT, Mills GB, and Kennedy JP, et al (2009). Loss of Phosphatase and Tensin homologue deleted on chromosome 10 engages ErbB3 and insulin-like growth factor-I receptor signaling to promote antiestrogen resistance in breast cancer. *Cancer Res* **69**, 4192–4201.

[22] Novartis Pharmaceuticals Corporation (2014). AFINITOR (everolimus) tablets for oral administration. AFINITOR DISPERZ (everolimus tablets for oral suspension). Hanover, NJ: Novartis Pharmaceuticals Corporation; 2014 .

[23] Baselga J, Campone M, Piccart M, Burris III HA, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, and Lebrun F, et al (2012). Everolimus in postmenopausal hormone receptor-positive advanced breast cancer. *N Engl J Med* **366**, 520–529.

[24] Yardley DA, Noguchi S, Pritchard KI, Burris III HA, Baselga J, Gnant M, Hortobagyi GN, Campone M, Pistilli B, and Piccart M, et al (2013). Everolimus plus exemestane in postmenopausal patients with HR+ breast cancer: BOLERO-2 final progression-free survival analysis. *Adv Ther* **30**, 870–884.

[25] Pritchard KI, Burris III HA, Ito Y, Rugo HS, Dakhil S, Hortobagyi GN, Campone M, Csöszi T, Baselga J, and Puttawibul P, et al (2013). Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. *Clin Breast Cancer* **13**, 421–432.

[26] Campone M, Lebrun F, Noguchi S, Pritchard KI, Burris III HA, Beck JT, Ito Y, Yardley DA, Bachelot T, and Pistilli B, et al (2013). Efficacy of everolimus plus exemestane in patients who received prior chemotherapy for advanced breast cancer or recurred after adjuvant endocrine therapy in BOLERO-2. Presented at the American Society of Clinical Oncology Annual Meeting, Chicago IL, May 31–June 4; 2013.

[27] Beck JT, Hortobagyi GN, Campone M, Lebrun F, Deleu I, Rugo HS, Pistilli B, Masuda N, Hart L, and Melichar B, et al (2014). Everolimus plus exemestane as first-line therapy in HR+, HER2$^-$ advanced breast cancer in BOLERO-2. *Breast Cancer Res Treat* **143**, 459–467.

[28] Campone M, Bachelot T, Gnant M, Deleu I, Rugo HS, Pistilli B, Noguchi S, Shtivelband M, Pritchard KI, and Provencher L, et al (2013). Effect of visceral metastases on the efficacy and safety of everolimus in postmenopausal women with advanced breast cancer: Subgroup analysis from the BOLERO-2 study. *Eur J Cancer* **49**, 2621–2632.

[29] Noguchi S, Masuda N, Iwata H, Mukai H, Horiguchi J, Puttawibul P, Srimuninnimit V, Tokuda Y, Kuroi K, and Iwase H, et al (2014). Efficacy of everolimus with exemestane versus exemestane alone in Asian patients with HER2-negative, hormone-receptor-positive breast cancer in BOLERO-2. *Breast Cancer* **21**, 703–714.

[30] Hortobagyi G, Noguchi S, Neven P, Heng DYC, Brechenmacher T, Ringeisen F, and Bachelot T (2014). Everolimus plus exemestane in patients with advanced invasive lobular carcinoma: efficacy and safety results from BOLERO-2.

Presented at the American Society of Clinical Oncology Breast Cancer Symposium (ASCO-BCS), San Francisco, CA, September 4–6; 2014.

[31] Burris H, Gnant M, Hortobagyi G, Hart L, Yardley DA, Eakle J, Provencher L, Brechenmacher T, Saletan S, and Taran T, et al (2013). Characterization of response to everolimus in BOLERO-2: A phase III trial of everolimus plus exemestane in postmenopausal women with HR+, HER2– advanced breast cancer. Abstract P2-16-17. Presented at the 36th Annual San Antonio Breast Cancer Symposium, December 10–14; 2013.

[32] Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, Noguchi S, Perez A, Rugo HS, and Deleu I, et al (2014). Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. *Ann Oncol* **25**, 2357–2362.

[33] American Cancer Society (2012). Breast Cancer Facts and Figures 2011–2012. Atlanta, GA: American Cancer Society; 2012 .

[34] Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, and Tatalovich Z, et al (2010). SEER Cancer Statistics Review, 1975–2008. National Cancer Institute Web site, available at: http://seer.cancer.gov/csr/1975_2008; 2010 . [April 22, 2011. Accessed October 21, 2014].

[35] Vetter M, Huang DJ, Bosshard G, and Guth U (2013). Breast cancer in women 80 years of age and older: a comprehensive analysis of an underreported entity. *Acta Oncol* **52**, 57–65.

[36] Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C, Hurria A, Extermann M, Girre V, and Brain E, et al (2007). Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. *Lancet Oncol* **8**, 1101–1115.

[37] Rosa Mendoza ES, Moreno E, and Caguioa PB (2013). Predictors of early distant metastasis in women with breast cancer. *J Cancer Res Clin Oncol* **139**, 645–652.

[38] Solomayer EF, Diel IJ, Meyberg GC, Gollan C, and Bastert G (2000). Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Res Treat* **59**, 271–278.

[39] Mundy GR (2002). Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer* **2**, 584–593.

[40] Santen RJ (2011). Clinical review: effect of endocrine therapies on bone in breast cancer patients. *J Clin Endocrinol Metab* **96**, 308–319.

[41] Gnant M, Baselga J, Rugo HS, Noguchi S, Burris HA, Piccart M, Hortobagyi GN, Eakle J, Mukai H, and Iwata H, et al (2013). Effect of everolimus on bone marker levels and progressive disease in bone in BOLERO-2. *J Natl Cancer Inst* **105**, 654–663.

[42] Korhonen T, Kuukasjarvi T, Huhtala H, Alarmo EL, Holli K, Kallioniemi A, and Pylkkänen L (2013). The impact of lobular and ductal breast cancer histology on the metastatic behavior and long term survival of breast cancer patients. *Breast* **22**, 1119–1124.

[43] Arpino G, Bardou VJ, Clark GM, and Elledge RM (2004). Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. *Breast Cancer Res* **6**, R149-156.

[44] Burris III HA, Lebrun F, Rugo HS, Beck JT, Piccart M, Neven P, Baselga J, Petrakova K, Hortobagyi GN, and Komorowski A, et al (2013). Health-related quality of life of patients with advanced breast cancer treated with everolimus plus exemestane versus placebo plus exemestane in the phase 3, randomized, controlled, BOLERO-2 trial. *Cancer* **119**, 1908–1915.

[45] Meisel JL, Domchek SM, Vonderheide RH, Giobbie-Hurder A, Lin NU, Winer EP, and Partridge AH (2012). Quality of life in long-term survivors of metastatic breast cancer. *Clin Breast Cancer* **12**, 119–126.

[46] National Comprehensive Cancer Network, Inc (2014). NCCN Clinical Practice Guidelines in Oncology. *Breast Cancer* [Version 3].

[47] Campone M, Beck JT, Gnant M, Neven P, Pritchard KI, Bachelot T, Provencher L, Rugo HS, Piccart M, and Hortobagyi GN, et al (2013). Health-related quality of life and disease symptoms in postmenopausal women with HR+, HER2$^-$ advanced breast cancer treated with everolimus plus exemestane versus exemestane monotherapy. *Curr Med Res Opin* **29**, 1463–1473.

[48] Hortobagyi G, Piccart M, Rugo H, Burris III H, Campone M, Noguchi S, Perez A, Deleu I, Shtivelband M, and Provencher L, et al (2013). Correlation of molecular alterations with efficacy of everolimus in hormone receptor–positive, HER2-negative advanced breast cancer: results from BOLERO-2. Abstract LBA509. Presented at the American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2013, Chicago, IL, USA; 2013.

[49] Rugo HS, Pritchard KI, Gnant M, Noguchi S, Piccart M, Hortobagyi G, Baselga J, Perez A, Geberth M, and Csoszi T, et al (2014). Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. *Ann Oncol* **25**, 808–815.

[50] Paplomata E, Zelnak A, and O'Regan R (2013). Everolimus: side effect profile and management of toxicities in breast cancer. *Breast Cancer Res Treat* **140**, 453–462.

[51] Porta C, Osanto S, Ravaud A, Climent MA, Vaishampayan U, White DA, Creel P, Dickow B, Fischer P, and Gornell SS, et al (2011). Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma. *Eur J Cancer* **47**, 1287–1298.

[52] Moldawer NP and Wood LS (2010). Management of key adverse events associated with everolimus therapy. *Kidney Cancer J* **8**, 51–59.

[53] Pilotte AP, Hohos MB, Polson KM, Huftalen TM, and Treister N (2011). Managing stomatitis in patients treated with mammalian target of rapamycin inhibitors. *Clin J Oncol Nurs* **15**, E83-89.

[54] Rugo HS, Pritchard KI, Gnant M, Noguch S, Piccart M, Hortobagyi GN, Burris HA, Vittori L, Sahmoud T, and Baselga J (2012). Everolimus (EVE) for postmenopausal women with advanced breast cancer (ABC) refractory to letrozole or anastrozole: long-term efficacy and safety results of the BOLERO-2 trial. Presented at the 8th European Breast Cancer Conference; Vienna, Austria, March 21–24; 2012.

[55] Sonis S, Treister N, Chawla S, Demetri G, and Haluska F (2010). Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. *Cancer* **116**, 210–215.

[56] Martins F, de Oliveira MA, Wang Q, Sonis S, Gallottini M, George S, and Treister N (2013). A review of oral toxicity associated with mTOR inhibitor therapy in cancer patients. *Oral Oncol* **49**, 293–298.

[57] de Oliveira MA, Martins E, Martins F, Wang Q, Sonis S, Demetri G, George S, Butrynski J, and Treister NS (2011). Clinical presentation and management of mTOR inhibitor-associated stomatitis. *Oral Oncol* **47**, 998–1003.

[58] Sankhala K, Mita A, Kelly K, Mahalingam D, Giles F, and Mita M (2009). The emerging safety profile of mTOR inhibitors, a novel class of anticancer agents. *Target Oncol* **4**, 135–142.

[59] White DA, Camus P, Endo M, Escudier B, Calvo E, Akaza H, Uemura H, Kpamegan E, Kay A, and Robson M, et al (2010). Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. *Am J Respir Crit Care Med* **182**, 396–403.

[60] Balagula Y, Rosen A, Tan BH, Busam KJ, Pulitzer MP, Motzer RJ, Feldman DR, Konner JA, Reidy-Lagunes D, and Myskowski PL, et al (2012). Clinical and histopathologic characteristics of rash in cancer patients treated with mammalian target of rapamycin inhibitors. *Cancer* **118**, 5078–5083.

[61] Soefje SA, Karnad A, and Brenner AJ (2011). Common toxicities of mammalian target of rapamycin inhibitors. *Target Oncol* **6**, 125–129.

[62] Wullschleger S, Loewith R, and Hall MN (2006). TOR signaling in growth and metabolism. *Cell* **124**, 471–484.

[63] Busaidy NL, Farooki A, Dowlati A, Perentesis JP, Dancey JE, Doyle LA, Brell JM, and Siu LL (2012). Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. *J Clin Oncol* **30**, 2919–2928.

[64] Wilson S and Chia SK (2013). Treatment algorithms for hormone receptor-positive advanced breast cancer: applying the results from recent clinical trials into daily practice—insights, limitations, and moving forward. *Am Soc Clin Oncol Educ Book* . doi:10.1200/EdBook_AM.2013.33.e20.

[65] Johnston SR (2012). BOLERO-2—will this change practice in advanced breast cancer? *Breast Cancer Res* **14**, 311.